IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Cyrus Rustam Kumana and Yok-Lam Kwong

Serial No.: 10/669,869 Art Unit: 1616

Filed: September 23, 2003 Examiner: Frank I. Choi

For: *FORMULATION OF ORAL COMPOSITIONS COMRISING ARSENIC TRIOXIDE AND METHODS OF USE THEREOF*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

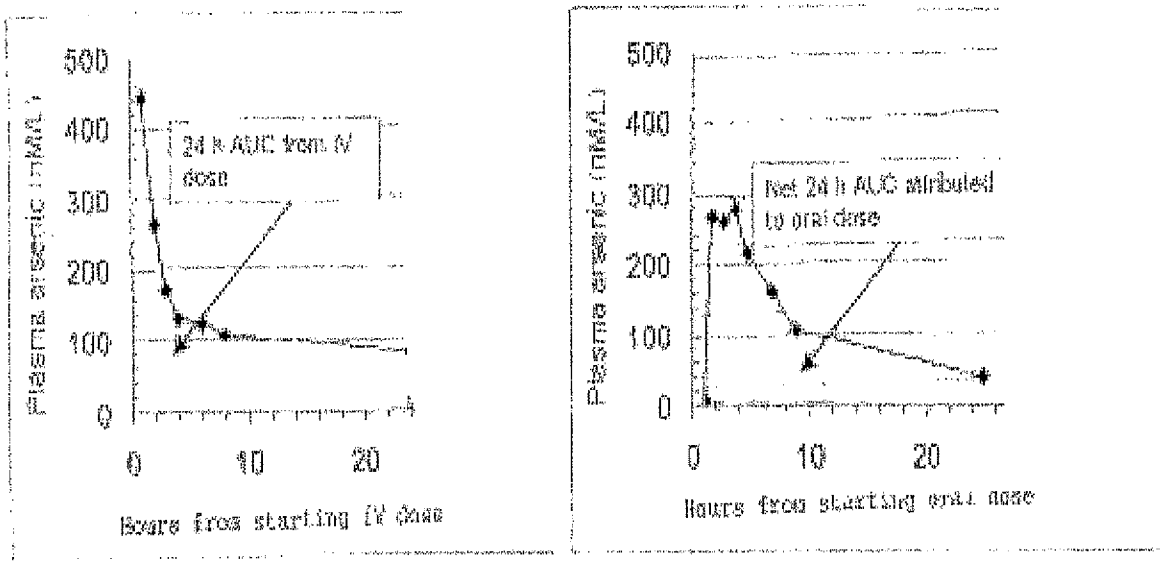
SECOND DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

We, the undersigned, Cyrus Rustam Kumana and Yok-Lam Kwong do hereby declare and state that:

1. We are co-inventors of the above-identified application. We affirm the statements made in our previously submitted Declaration under 37 C.F.R. 1.132.

2. The following figures are derived from the plasma levels measured after IV and oral doses of 10 mg each to a human patient with cancer.



3. As can be seen from the figures of the plasma level versus time plots, when the same dose of 10 mg of arsenic trioxide is given orally instead of IV to the same individual:

a. The total bioavailability (area under the curve) is virtually the same, but

b. The peak plasma level after oral administration is about half as high as the peak level occurring after IV dosing.

4. The arrythmogenic toxicity, i.e., effect on QT interval, of arsenic trioxide is concentration dependent, and therefore maximum at peak plasma concentrations. In contrast, the efficacy of arsenic trioxide against leukemia depends on the total amount entering/available to the body, i.e., bioavailability, and is represented by the area under the curve (AUC). Therefore, when used orally, any given dose of arsenic-trioxide appears to be much safer with respect to the risk of inducing cardiac rhythm disturbances, than after IV dosing, while its beneficial effects against leukemia are the same.

5. In clinical practice, the usual daily dose of intravenous (IV) arsenic trioxide is 0.15 mg/kg. The doses of oral arsenic trioxide vary between 5-10 mg daily. However, intravenous arsenic trioxide sometimes entails the administration of far higher dosages,

up to two to four times those used conventionally. Under these circumstances, the enhanced cardiac safety of our oral formulation is particularly advantageous.

6. We declare that all statements made herein are to our knowledge and belief true and that all statements made on available information and beliefs are believed to be true, and further, that the statements are made with the knowledge that willful false statements are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 18-9-07

Cyrus Rustam Kumana

Date: 18-9-07

Yok-Lam Kwong